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10/802,249	03/17/2004	Ralf Mauritz	21718 US-as	5270
23690 7590 08/20/2009 ROCHE DIAGNOSTICS OPERATIONS INC. 9115 Hague Road Indianapolis, IN 46250-0457				
EXAMINER				
LIU, SUE XU				
ART UNIT		PAPER NUMBER		
1639				
NOTIFICATION DATE		DELIVERY MODE		
08/20/2009		ELECTRONIC		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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# Office Action Summary

## Application No.

10/802,249

## Applicant(s)

MAURITZ ET AL.

## Examiner

SUE LIU

## Art Unit

1639

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 09 June 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 1-3, 12, 13 and 15-22 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-3, 12, 13, and 15-22 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- 1) ☐ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB-08)  
Paper No(s)/Mail Date \_\_\_\_\_
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

#### ***Continued Examination Under 37 CFR 1.114***

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(c), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(c) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6/9/09 has been entered.

#### ***Claim Status***

2. Claims 4-11, 14 and 23-26 have been cancelled.  
Claims 1-3, 12, 13, and 15-22 are currently pending.  
Claims 1-3, 12, 13 and 15-22 are being examined in this application.

#### ***Election/Restrictions***

3. Applicant's election without traverse of Group I (Claims 1-22) in the reply filed on 10/18/06 is as previously acknowledged.
4. Applicant's election without traverse of the following species:  
A.) nucleic acids for the biopolymers;  
B.) fluorescent groups, specifically, stilbene, as the detectable protecting groups;  
C.) Compound (f) in Figure 5 as the core structure;  
in the reply filed on 10/18/06 and 3/6/07 is as previously acknowledged.

***Priority***

5. This application claims foreign priority to EPO 03006098.2 (3/19/03).
6. Receipt is as previously acknowledged of papers submitted under 35 U.S.C. 119(a)-(d), which papers have been placed of record in the file.

***Claim Rejections Maintained***

***Claim Rejections - 35 USC § 103***

7. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

8. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

**McGall and Others**

9. Claims 1-3, 12, 13 and 15-22 are rejected under **35 U.S.C. 103(a)** as being unpatentable over **McGall et al** (US 6,238,862; 05/29/2001), **Wagner et al** (Helvetic Chimica Acta. Vol. 80: 200-212. 1997; cited in IDS filed on 9/22/04), in view of **Hobbs et al** (5,151,507; 9/29/1992;

cited previously), **Chen** et al (*Journal of Organic Chemistry*. Vol. 66: 1725-1732; 2001; cited previously) and **Agris** (PGPUB 20020045167; 4/18/2002; cited previously). The previous rejection is maintained for the reasons of record as set forth in the previous Office action as well as for the reasons below.

The instant claims recite a “quality control method for achieving complete deprotection of protected reactive groups in on-chip synthesis of a biopolymer array, the method comprising

(a) synthesizing a plurality of different biopolymer species on an array from monomeric or oligomeric building blocks comprising detectable protecting groups coupled directly to amino groups of the nucleotide building blocks and the detectable protecting groups remain coupled until synthesis of the biopolymer array,

(b) taking one or more steps to cleave the detectable protecting groups,

(c) determining a degree of deprotection by detecting detectable protecting groups remaining on the array after cleavage, and

(d) repeating steps (b) and (c) until detectable protecting groups are no longer detected, indicating that complete deprotection is achieved, wherein the quality control method is performed entirely on-chip.”

**McGall et al**, throughout the patent, teach methods of quality control for manufacturing nucleic acid probe arrays (e.g. Abstract and Claim 1 of the reference), which reads on the quality control method of **clm 1**.

The reference teaches synthesizing nucleic acids using protected monomers such as 5' and 3' protected nucleotides (e.g. Claims 5, 12 and 23; col. 2, lines 40+; Figures 9-10; col.4, lines 51+), which reads on synthesizing biopolymer on an array using protected monomers of

step (a) of **clm 1** and nucleic acids of **clm 12**. The instant claim 1 recites “until synthesis of the biopolymer array”, which can be broadly and reasonably interpreted to mean during any stage of the “synthesis” of the biopolymer array (i.e. can be the beginning, middle or end of the biopolymer array synthesis.)

The reference teaches “deprotecting” (or removal) of the protecting group at the end of each round of synthesis (e.g. Claim 23; col. 2, lines 40+; Figure 9), which reads on the cleaving the protecting group of step (a) of **clm 1**. The reference teaches, for example, “photolabile groups” (i.e. protection groups) and “side chain protective groups” are removed after the desired products are produced (i.e. the desired product would be the complete oligonucleotide array; e.g. col.5, lines 2), which reads on the step of cleaving the protecting groups as recited in step (b) of **clm 1**.

The reference teaches “determining the amount of unprotected active sites” (col. 2, lines 49+) by detecting the amount “detectable labels” on the array (col. 2, lines 40+; cols. 8-9; Figure 7; especially, col.9, lines 9+), which reads on step (c) of **clm 1**.

The reference also teaches repeating steps of “deprotection” (e.g. claim 12), which reads on the repeated deprotection step (step (d)) of **clm 1**.

The reference teaches the detectable label (or protecting label) is a fluorescent label such as a rhodamine (e.g. Claims 26 and 27 of the reference), which reads on the “fluorescent groups” of **clm 2** and rhodamine of **clm 3**.

The reference teaches the fluorescent label is linked (or coupled) to the nucleotide (e.g. Figure 6). The reference teaches linking the fluorescent label through the phosphate group in the sugar group of the nucleotide (e.g. Figure 6).

McGall et al do not explicitly teach the protection groups are directly coupled to and protect the nucleobase amino groups as recited in the amended **clms 1 and 13**. The reference also does not explicitly teach the repeating steps of deprotection and detection (until “completion”) as recited in the amended **clm 1**. The reference also does not teach using “stilbene” (the elected species) as the “fluorescent group”, as recited in **clm 3**. The reference also does not explicitly teach the various chemistries recited in **clms 15-22**.

However, McGall et al., teach repeating steps of “deprotection” (e.g. claim 12). It would have been prima facie obvious for one of ordinary skill in the art to repeat both the deprotection and detection steps for the desired results measuring deprotection at different stages. It would have been obvious to one of ordinary skill in the art to apply the standard technique of repeating deprotection and detection steps as the procedure for performing the said steps are taught by McGall, to improve the deprotection (such as to render various degrees of deprotection) and detection (such as to generate an average measurements) for the predictable result of enabling standard oligonucleotide synthesis and the accompanying quality control measurements.

**Wagner et al**, throughout the publication, teach methods of nucleic acid synthesis using protected nucleotides. (see Abstract). The reference teaches synthesis of various oligonucleotides using protected nucleotides (pp. 204-206; especially Table 1 and p. 204, last para). The reference teaches the fluorescent label is linked directly to the amino group of the nucleobases (e.g. p. 202, Schemes 1-2), which reads on the “coupled to nucleobases” of **clm 13**, and coupling through the amino groups of **clm 1**. The reference also teaches detecting the protecting groups attached to the synthesized oligonucleotides (e.g. pp.206-207). The reference also teaches deprotecting the label

attached nucleobase after the synthesis of the oligonucleotide (e.g. pp.205-206; Figure on pg.206).

The reference teaches the detectable label (or protecting label) is a fluorescent label such as a “dnsecoc” (or a “dansyl”) (e.g. p. 201, para 3 and Figures), which reads on the “fluorescent groups” of **clm 2** and “dansyl” of **clm 3**. The “dnsecoc” ((dansylethoxy)carbonyl) group also reads on the “L” group when n=1 (as recited in **clm 21**), because the carbonyl group reads on the formula “C(O)” and the dansyl group reads on formula “R”.

The reference also teaches the structure of nucleotides comprising a base (protected by dnsecoc), a sugar, a protected hydroxyl group, and a protected phosphate group (e.g. Scheme 2, Scheme 5). The (MeO)<sub>2</sub>TrO (or Dimethoxytrityl) group in Scheme 5 of the reference (see p. 201, para 4 and p. 204) reads on the hydroxyl protection group, DMTrO (the elected species of ; see Reply, filed 3/6/07, p. 2) or the “triphenylmethyl” group of **clms 15, 16, and 17**.

The reference also teaches phosphate protection group such as the “(2-cyanoethoxy)bis(diisopropylamino)phosphine” at the 3’ sugar position (p. 204, para 1 and Scheme 5), which is the same phosphoramidite (phosphate amide) (i.e. the R3, R4, R5 and R6 groups of compound (f) in Figure 5 (the instant elected species; Reply, filed 3/6/07)), as recited in **clms 18, 19, and 20**.

The reference also teaches various nucleobases such as C, A, and G (e.g. p. 204, Scheme 5), which read on the nucleotide bases recited in **clm 22** and the elected species of adenine.

**Agris**, teaches methods of monitoring the degree of deprotection “after” synthesis of oligonucleotides on arrays by detecting detectable protecting groups “on the array” (e.g. Abstract; claims 14-18, 45 and 51; p.9, [0158]±). The reference also teaches the protecting group



is attached to the nucleotide base through the amino group of the base (e.g. p.5, [0046]+). The reference also teaches the need for such detection so that simple and reliable techniques for determining the purity of the desired oligonucleotides can be carried out (e.g. p.1, [0005]).

**Hobbs et al** teach using various fluorescent molecules to label (or protect) nucleotides (see Abstract). The reference teaches “stilbene” can be used to attach to the nucleobases (col. 30, lines 20+) through linkers that comprise “carbonyl” group (reads on the formula of “COR” of **clm 21**; col. 11, lines 50+). The reference also teaches various fluorescent dyes can be used depending on the different applications (cols. 12+).

In addition, **Chen et al**, teaches attaching “stilbene” to nucleosides (see Abstract). The Chen reference also teaches “stilbene” has “bright fluorescence of very high quantum yield” (p. 1725, right col., para 2).

Therefore, it would have been prima facie obvious for one of ordinary skill in the art at the time the invention was made to attach a fluorescent group such as “stilbene” to a “monomeric building block” (such as a nucleoside) to the amino groups of the nucleobase for various assays such as detecting the attached fluorescent group on an oligonucleotide array.

A person of ordinary skill in the art would have been motivated at the time of the invention to couple the protection group to the amino group of the nucleobase, because the nucleobase protection groups offer the advantages of providing more efficient and fast working oligodeoxyribonucleotide synthesis, as taught by Wagner et al (e.g. p.200). In addition, because both the McGall reference and the Wagner reference teach methods of using protected monomers (nucleotide building blocks) to generate oligonucleotides with detection of the degree of deprotection (for either the sugar phosphate groups or the nucleobase groups) that are

necessary for completion of oligonucleotide synthesis, it would have been obvious to one skilled in the art to substitute one detection method of detecting the deprotection of the sugar phosphate reactive groups for the other (the deprotection of the nucleobase groups) to achieve the predictable result of determining the degree of deprotection for a solid state oligonucleotide synthesis. In addition, the Agris reference teaches detecting the degree of deprotection after oligonucleotide array synthesis by measuring the amount of the protecting groups "remaining on the array" (i.e. on-chip analysis), as discussed supra. The Agris reference also teaches the need for such on-chip detection so that simple and reliable techniques for determining the purity of the desired oligonucleotides on an array can be achieved. Thus, it would have been obvious to one skilled in the art to substitute one detection method (such as using antibody recognition on the array) for the other (fluorescence detection on the array) to achieve the predictable result of detecting the protecting group remaining attached to the nucleotide bases on the synthesized oligomer array to improve the quality control method for array synthesis.

A person of ordinary skill in the art would also have been motivated at the time of the invention to directly detect the remaining detectable protecting group on an array to assess the purity of the synthesized oligonucleotides, because Agris teaches the need for such as a simple and reliable technique to control the quality of the synthesized microarray, as discussed supra. In addition, it would have been prima facie obvious for a person of ordinary skill in the art to use fluorescent groups (such as stilbene) as the protecting group and to measure the remaining fluorescent signals after cleavage to assess the degree of protection, to improve the quality control assay for the deprotection step during an array generation (of methods such as McGall et

al) for the predictable result of enabling routine oligonucleotide synthesis on an array with various known protection and labeling groups.

A person of ordinary skill in the art would have been motivated at the time of the invention to use “stilbene” as the “detectable protecting group”, because “stilbene” is a known fluorescent label for biomolecules (especially nucleotides), and stilbene is known to exhibit “bright blue fluorescence of very high quantum yield”, as taught by both Hobbs et al and Chen et al.

A person of ordinary skill in the art would have been motivated at the time of the invention to use the specific nucleotide building blocks and their corresponding chemistry to generate the required reagent for the method of detecting deprotection, because the structures for basic nucleotide building blocks are known in the art, and the various protection groups are known and routine in the art as taught by Wagner et al. In addition, Wagner et al also teach the advantages of using these nucleotide building blocks and their corresponding protection groups, including providing efficient and fast working oligonucleotide synthesis as well as fast and effective cleavage of the protection group (e.g. pp.200-201).

A person of ordinary skill in the art would have reasonable expectation of success of achieving such modifications since McGall et al, Wagner et al, Hobbs et al and Chen et al have demonstrated successful attachment of various protection groups such as fluorescent groups (especially stilbene) to nucleosides through known reaction mechanisms (such as the formation of -HN-C=O linkage between the nucleobases and the stilbene molecule) as well as using various nucleotide building blocks to build oligonucleotides, as demonstrated by the said references.

Discussion and Answer to Argument

10. Applicant's arguments have been fully considered but they are not persuasive for the following reasons (in addition to reasons of record). Each point of applicant's traversal is addressed below (applicant's arguments are in *italic*):

Applicants' arguments are addressed with the following discussion as well as the above modified rejection (in light of applicant's amendment to the claims).

*In general, applicants traversed the above rejection over a combination of references by attacking each reference alone. (Reply, pp.7+).*

In response to applicant's arguments against the references individually, one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

*Applicants assert the "Wagner and Agris" references "illustrate methods relating to off-chip synthesis of oligonucleotide arrays..." (Reply, p.7, para 4; p.9, para 3+).*

Contrary to applicant's assertion, at least the Agris reference teaches on-chip detection of deprotection, as it is explicitly claimed and recited in the Agris publication (see, for examples, claims 14-18, 45 and 51; p.9, [0158] +). Applicants are also respectfully directed to the above modified rejection for reasons to combine the cited references and how the combination of the cited references teaches all elements.

Applicants allege the Agris reference only teach off-support analysis. However, applicants do not provide specific citation for these alleged teachings. Applicants also allege various teachings of the Agris reference (such as “not offer the practitioner any specific guidance...”). However, the relevance of these discussion in term so the outstanding 103 rejection is not clear.

*Applicants argue the McGall reference does not teach all elements of the instant claims and the McGall reference is then only reference cited that “addresses the problems associated with quality control...” (Reply, p.8, para 2+).*

However, the above rejection is not over the McGall reference alone. Applicants are respectfully directed to the above rejection for detailed discussion how the combination of the reference teaches all elements of the instant claims. The alleged deficiency of the McGall reference is remedied by the above cited additional references (especially the Agris and Wagner references).

*Applicants also assert the Wagner reference does not teach “use of fluorescence at the base-coupling to monitor a degree of deprotection or for quality control purpose...” (Reply, p.9, para 1).*

However, the above rejection is not over the Wagner reference alone. As discussed above, the Wagner reference teaches detecting the protecting groups attached to the synthesized oligonucleotides (e.g. pp.206-207). The reference also teaches deprotecting the label attached nucleobase after the synthesis of the oligonucleotide (e.g. pp.205-206; Figure on pg.206). Thus,

the Wagner reference supplies the missing element of using nucleotides with protected nucleobases (through the amino groups) for oligonucleotide synthesis, and the element of cleaving the detectable protecting group. Thus, it would have been prima facie obvious to use the detectable nucleobase protecting group in the quality control method of McGall.

***New Claim Objection(s) / Rejection(s)***

***Claim Rejections - 35 USC § 112***

11. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

12. Claims 1-3, 12, 13 and 15-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites the limitation "the nucleotide building blocks" in step (a). There is insufficient antecedent basis for this limitation in the claim.

***Conclusion***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Sue Liu whose telephone number is 571-272-5539. The examiner can normally be reached on M-F 9am-3pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached at 571-272-0951. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/SUE LIU/  
Patent Examiner, Art Unit 1639  
8/12/09